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Hypoxia and hypoxia response-associated molecular markers in esophageal cancer: A systematic review

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ABSTRACT

Purpose: In this systematic review, the existing evidence of available hypoxia-associated molecular response biomarkers in esophageal cancer (EC) patients is summarized and set into the context of the role of hypoxia in the prediction of esophageal cancer, treatment response and treatment outcome.
Methods: A systematic literature search was performed in Web of Science, MEDLINE, and PubMed databases using the keywords: hypoxia, esophagus, cancer, treatment outcome and treatment response. Eligible publications were independently evaluated by two reviewers. In total, 22 out of 419 records were included for systematic review. The described search strategy was applied weekly, with the last update being performed on April 3rd, 2017.
Results: In esophageal cancer, several (non-)invasive biomarkers for hypoxia could be identified. Independent prognostic factors for treatment response include HIF-1α, CA IX, GLUT-1 overexpression and elevated uptake of the PET-tracer ^{18}F-fluoroerythronitroimidazole (^{18}F-FETNIM). Hypoxia-associated molecular responses represents a clinically relevant phenomenon in esophageal cancer and detection of elevated levels of hypoxia-associated biomarkers and tends to be associated with poor treatment outcome (i.e., overall survival, disease-free survival, complete response and local control).
Conclusion: Evaluation of tumor micro-environmental conditions, such as intratumoral hypoxia, is important to predict treatment outcome and efficacy. Promising non-invasive imaging-techniques have been suggested to assess tumor hypoxia and hypoxia-associated molecular responses. However, extensive validation in EC is lacking. Hypoxia-associated markers that are independent prognostic factors could potentially provide targets for novel treatment strategies to improve treatment outcome. For personalized hypoxia-guided treatment, safe and reliable makers for tumor hypoxia are needed to select suitable patients.

Contents

Abbreviations: AC, adenocarcinoma; ARCON, accelerated radiotherapy with carbogen breathing and nicotinamide; CA IX, carbonic anhydrase; CCRT, concurrent chemoradiotherapy; CR, complete response; Cu-ATSM,, copper-62 labeled diacetyl-bis (N4-methylthiosemicarbazone); DFS, disease-free survival; EC, esophageal cancer; ESCC, esophageal squamous cell carcinomas; 18F-FAZA,, 18F-fluoroazomycin arabinoside; 18F-FETA,, [18F]fluoroetanidazole; 18F-FETNIM, 18F-fluoroerythronitroimidazole; 18F-FMISO, 18F-fluoromisonidazole; 18F-HX4, 18F-3-fluoro-2-(4-((2-nitro-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-1-ol; GLUT-1, glucose-transporter-1; HAP, hypoxia-activated prodrug; HIF, hypoxia-inducible factor; HRE, hypoxia response element; LC, local control; MESH, Medical Subject Headings; MRI, magnetic resonance imaging; OE-MRI, oxygen-enhanced magnetic resonance imaging; OS, overall survival; PET, positron-emission tomography; PDT, photodynamic therapy; ROS, reactive oxygen species; SUV, standard uptake values; VEGF, vascular endothelial growth factor.

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1. Introduction

Hypoxia is one of the hallmarks of cancer and has been associated with a more aggressive tumor phenotype, a higher likelihood of metastatic progression and resistance to (chemo)radiotherapy [1]. Hypoxia occurs when tissue oxygen demand (e.g., increased metabolism) exceeds oxygen supply (e.g., acute and/or chronic vascular changes, anemia, malfunctioning hemoglobin). In normal tissue, acute hypoxia (i.e., perfusion-limited) is resolved by physiological homeostasis while in cancerous tissue, additional chronic hypoxia (i.e., diffusion-limited) is more likely to manifest. The rapid and uncontrollable tumor growth requires large amounts of nutrients and therefore triggers neo-angiogenesis. However, the resulting tumor neo-vasculature is highly chaotic and inefficient. Oxygenation of tumor regions surrounding perfused blood vessels therefore depends on a diffusion-gradient, relative to the intravascular oxygen partial pressure (pO_2). Generally, the diffusion-gradient is limited to 100–180 μm, thus inducing chronic hypoxia in remote regions [1].

Clinically, hypoxia is thought to be a key factor contributing to treatment resistance and poor patient prognosis [2]. Although neoadjuvant therapy (i.e., CROSS regimen with weekly carboplatin (2 mg/ml/min AUC) and paclitaxel (50 mg/m^2) for 5 weeks, concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week), followed by surgery) has been proven to be valuable in esophageal cancer (EC), prognosis remains dismal with approximately 20% complete responders (5 yr overall survival = 20–30% [3,4]), making EC the sixth most lethal cancer type in 2012, worldwide [5]. In 2016, over 15.000 patients died from EC in the USA alone [5]. Most EC contain hypoxic areas with a higher percentage in the adenocarcinomas, potentially explaining the poor treatment outcome for these patients [6]. About half of the patients treated with definitive chemoradiation will suffer from a locoregional recurrence. For effective radiation treatment, the presence of molecular oxygen is essential. Under normoxic conditions, ionizing radiation leads to the formation of free radicals and reactive oxygen species (ROS), which can damage DNA. Free radicals produced in the critical target can be fixed in the presence of oxygen, leading to irreversible DNA damage. In hypoxic conditions however, free radicals are reduced and hypoxic regions becomes 2–3 times more radio-resistant, which may explain low rates of complete response (CR) and local control (LC) [1,7]. Accordingly, patients with hypoxic EC might need a different, personalized treatment approach to reach therapeutic success.

Since tumor hypoxia cannot be predicted based on clinical size, stage, or grade, there is a need for molecular biomarkers that can assess hypoxic status in EC. Such biomarkers could be used to detect hypoxic tumor status at an early stage, evaluate treatment response, predict prognosis in EC patients and select patients for suitable, personalized treatment options.

In this systematic review, we provide an overview of hypoxia response-associated biomarkers in EC patients and aim to evaluate the prognostic value of elevated expression rate of hypoxia-associated biomarkers with regard to treatment outcome and efficacy [i.e., overall survival (OS), disease-free survival (DFS), CR, and LC]. Markers that are independent prognostic factors could potentially provide targets for novel treatment strategies. In addition, several known methods to improve treatment outcome will be discussed in relationship to these hypoxia-associated biomarkers.

2. Material and methods

2.1. Systematic search strategy

The research question for this systematic review was defined as: "What are the known hypoxia-associated molecular markers in patients with EC and how does elevated expression associate with treatment outcome and response?".

To consider the research question, a comprehensive PRISMA-based literature search was performed to identify relevant studies published in PubMed (National Center for Biotechnology Information, NCBI), MEDLINE (U.S. National Library of Medicine, using NCBI), or Web of Science (Thomson Reuters). The electronic databases were explored using a PICOS-based search string containing a free-text or Medical Subject Headings (MeSH) construction of 5 key search terms: 'hypoxia' AND 'esophagus' AND 'cancer' AND ('treatment outcome' OR 'treatment efficacy'). For each search term, all known synonyms and associated keywords were included in the search string using Boolean OR-operators. A detailed description of the entire search strings can be found in Appendix A1 [8]. The complete search strategy was applied weekly, with the last update being performed on April 3rd, 2017.

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